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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,265	11/04/2003	Brenda F. Baker	ISIS-5300	7033

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
12/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,265	BAKER ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *120,121,124-128,131-133,136-154 and 157-167* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *120, 121, 124, 127, 136-140, 143, 148, and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Declaration of Dr. Corey*.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 125,126,128,131-133,141,142,144-147,150-154 and 157-167.

DETAILED ACTION

Remarks

Claims 1-119, 122, 123, 125, 126, 128-135, and 139-167 are canceled. Claims 120, 121, 124, 127, 136, 137, and 138 are pending and are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Inventorship

In view of the papers filed 08/18/2009, the inventorship in this nonprovisional application has been changed by the deletion of Brenda F. Baker, Anne B. Eldrup, Muthiah Monoharan, Balkrishen Bhat, Richard H. Griffey, and Eric E. Swayze.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 103 - Withdrawn

The rejection of claims 139, 140, 143, 148, and 149 is withdrawn because the claims have been canceled.

Claim Rejections - 35 USC § 103 - Maintained

Claims 120, 121, 124, 127, 136, 137, and 138 are rejected under 35 U.S.C. 103(a) as

being unpatentable over Lee, *et al.* (Cell 1993, vol. 75, pages 843-854), Manche, *et al.* (Molecular and Cellular Biology 1992, vol. 12, pages 5238-5248), Agrawal, *et al.* (WO 94/01550, item 269 on 04/04/2005 IDS) and Baracchini, *et al.* (US 5,801,154). This rejection is maintained for the reasons of record.

RESPONSE TO ARGUMENTS

Applicants traverse the obviousness rejection by providing a declaration from David Corey.

Lee, et al.

With regard to the Lee et al. reference, Dr. Corey argues that in order to arrive at a compound described in the claims starting with lin-4S one would have to change the base sequence to make it fully complementary to a target and pair it with a second, complementary strand to form a duplex; he states that Lee provides no reason for doing this. Dr. Corey further notes lin-4L is not a duplex of two separate strands and because this duplex is speculated to be inactive there would be no reason to change a stem-loop to a duplex. Dr. Corey states that the enzyme that separates the self-complementary portion of a stem-loop molecule may not be able to separate the strands of a duplex consisting of two unattached strands in order for a self-complementary molecule to function as an antisense compound. Dr. Corey further argues RNA is relatively unstable and susceptible to degradation by nucleases and argues that because a hairpin structure constrains the complementary portions to remain near one another, it likely enhances nuclease resistance and one would be disinclined to replace a relatively stable and

nuclease resistant structure with one that would be expected to be less stable and less resistant. Dr. Corey further states the duplex described in Lee et al. is an endogenous transcript and nothing suggests that an exogenous sequence could be used to achieve the same effect and there is no suggestion in the reference to introduce modifications into a synthetic molecule. Dr. Corey concludes that compounds having the structure in the claims would have been considered ill-suited for furthering or exploiting the research described in Lee.

These arguments with regard to the Lee et al. reference are not persuasive because they rely on the premise that the rejection of record is directed to changing the compounds disclosed by Lee into other compounds for use as an antisense compound. The rejection is not based on the teachings of Lee alone, but on a combination of references, and does not rely on a conversion of Lee from a partially complementary stem-loop to a fully complementary duplex. The teachings of Lee et al. are cited to demonstrate that, at the time of filing, RNAs that form duplex structures were known to those in the art and were used for a variety of purposes.

Manche, et al.

With regard to the Manche et al. reference, Dr. Corey argues Manche does not provide a reason to make duplexes comprising oligonucleotides 17 to 25 nucleosides in length, as recited in the present claims, because duplexes of that length failed to activate DAI and this reference further offers no reason to make chemically modified oligonucleotides because the duplexes used were synthesized enzymatically.

These arguments are not persuasive because Manche actually makes duplexes of oligonucleotides of 17-25 nucleotides in length; whether such compounds were able to activate

DAI is not at issue in this application; the claims are not directed to compounds having any particular activity. While it is correct the compounds of Manche were enzymatically synthesized, the reason to make chemically modified oligonucleotides comes from the knowledge in the art that stabilization of oligonucleotides is desirable. This knowledge is demonstrated by the teachings of Baracchini et al. and attested to by Dr. Corey in his remarks regarding the relative instability and nuclease susceptibility of RNA.

Baracchini, et al.

With regard to Baracchini et al., Dr. Corey argues that Baracchini does not provide a reason to make double-stranded compounds, which would be expected to be inactive as RNase-H based antisense compounds because the sense strand would interfere with the ability of the antisense oligonucleotide to hybridize with its intended target RNA, and that this reference does not provide a reason to make compounds comprising ribonucleotides. Dr. Corey notes that the present specification describes an antisense mechanism that does not depend on RNase H and it would have been impossible to make confident predictions regarding whether chemical modifications would assist or interfere with the function of RNase II1.

It is correct that Baracchini does not teach double stranded compounds and does not exemplify compounds comprised of RNA, but this reference is not relied upon for such teachings, which are found in the Lee, Manche, and Agrawal references. Also, the claims are directed to compounds, not to a mechanism of action, therefore whether one could predict an effect on the function of RNase III is not relevant to the rejection.

Agrawal, et al.

With regard to the Agrawal et al. reference, Dr. Corey argues this reference teaches single stranded self-complementary compounds that are covalently linked and Agrawal provides no reason to make a duplex comprising two separate oligonucleotides. Dr. Corey further argues that compound C in Figure 5, which most closely resembles the presently claimed duplexes, has a duplex region containing only 12 base-pairs, which is well below the minimum number of 17 in the present claims. Dr. Corey further argues Agrawal describes RNase-H dependent antisense compounds and the presently claimed compounds would not be considered suitable for use as RNase-H dependent antisense compounds.

These arguments are not persuasive because, as noted in the rejection, Agrawal does teach compounds that comprise two separate strands. The rejection is not based on compound C of figure 5; the teachings of the prior art are not limited to exemplified embodiments. Agrawal teaches at page 10 that the target hybridizing region is about 8 to about 50 nucleotides in length. Also, the instant compounds are not recited to have any particular use, therefore whether they would be suitable as RNase H dependent compounds is not relevant to the rejection.

Dr. Corey asserts the office action fails to offer a reason why one would make the claimed compounds, citing page 3 of the action. This assertion is incorrect; the reasons why the instant claims are obvious are described at page 5. Dr. Corey repeats the argument that Lee et al. and Agrawal et al. do not teach duplex RNAs and that these references therefore do not teach inhibition via duplex RNAs. The examiner notes that stem-loop structures do form a duplex in the self- complementary region and Agrawal does teach separate complementary strands as

described above, therefore the examiner stands by this statement.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak
Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635